costs were included, the average cost per quality adjusted life year amounted to € −17,441, but the uncertainty around both CE-ratios was substantial.
Conclusions: Over a period of 52 weeks, with a CE-ratio of – € 107,505 per QALY from the societal perspective and a CE-ratio of € −17,441 per QALY from the healthcare perspective, our study revealed a considerable probability that exercise therapy added to GP care is cost saving or cost effective as compared to GP care alone.

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RESULTS FROM A SINGLE CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF THE EFFICACY AND SAFETY OF INTRA-ARTICULAR ONABOTULINUMTOXINA FOR OSTEOARTHRITIS KNEE PAIN

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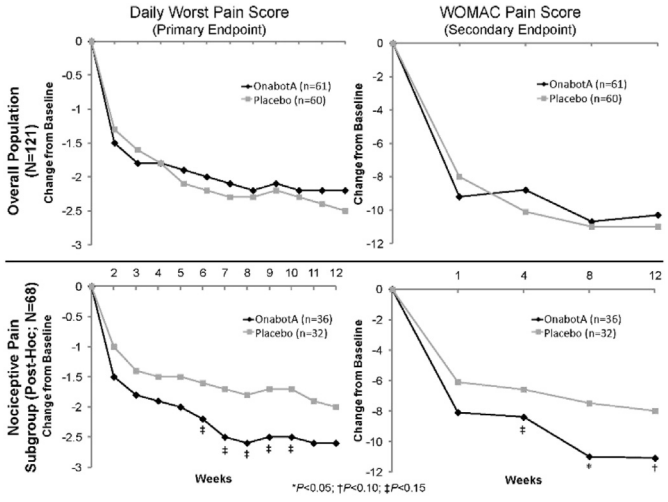
Purpose: The peripheral release of inflammatory mediators may sensitize nociceptors, provoke central sensitization, and facilitate clinical pain. Inhibition of the peripheral manifestations in knee osteoarthritis (OA) by onabotulinumtoxinA (onabotA) may reduce the drive, central consequences, and eventually clinical pain. Study objectives were to determine the safety and efficacy of a single intra-articular (IA) onabotA injection in patients (pts) with painful knee OA.
Methods: Pts 40–75 y with knee OA (American College of Rheumatology modified clinical classification criteria; Kellgren-Lawrence grade I-III) were enrolled in this 16-wk, single-center, double-blind, randomized, placebo-controlled, parallel-group phase 1b study. Pts were stratified by baseline 14-day average daily worst pain score (ADWP; 4.0–9.0 [0–10 numeric rating scale]), and randomized (1:1) to ultrasound-guided injection of either onabotA (200 U) or placebo (saline). Pts recorded worst daily pain for 2 wks before and 12 wks after injection (study visits: 1, 4, 8, 12 wks).
The planned primary efficacy assessment was 14-day ADWP score change from baseline, jointly analyzed for wks 4, 8, and 12 by repeated measures analysis of covariance (RMANCOVA); secondary planned efficacy outcomes included Western Ontario McMaster (WOMAC) OA Index (total, pain, and physical function scores) and pt global impression of change (GIC). Other planned outcomes included the Pain*DETECT* questionnaire (PD-Q), assessed at baseline and each visit. 3 pain subtypes have been defined by total PD-Q score: nociceptive (PD-Q score ≤12), neuropathic (≥19), and uncertain (≥13 and ≤18). Unplanned post-hoc analyses of primary and secondary outcomes by baseline PD-Q pain subtype were performed. Safety data were collected, including muscle strength around the knee (knee extension/flexion, ankle dorsiflexion/plantarflexion) for the study side and the contralateral side.
The primary efficacy assessment (intent-to-treat population) was analyzed using RMANCOVA for between-group comparisons, adjusted for baseline ADWP score. Secondary efficacy variables were analyzed with a Wilcoxon rank-sum test; WOMAC analyses did not use a baseline covariate. The safety population included all pts who received drug. All randomized pts received the assigned drug.
Results: Of 170 screened pts, 121 were randomized to onabotA (n = 61) or placebo (n = 60). Mean age was 62.3 y, all Caucasian, and comparable male (n = 59) and female (n = 62) participation. No clinically relevant between-group differences were observed at baseline.
The primary efficacy analysis yielded no significant difference between onabotA and placebo for the change from baseline in ADWP score to the 3 prospectively defined time points ($P = 0.70$). Between-group differences were also not significant for ADWP score change from baseline to each individual time point (each of wks 2–12), WOMAC (total index, pain, or physical function scores at wks 1, 4, 8, 12), or GIC (wks 1, 4, 8, 12). Post-hoc analyses by PD-Q pain subtype found numerically greater improvement for all efficacy outcomes among pts with nociceptive pain (PD-Q≤12) who received onabotA (n = 36) versus placebo (n = 32) across all time points (Figure); significant differences were seen at wk 8 and/or 12 for all WOMAC outcomes and GIC.
Adverse events (AEs) were reported for 24 pts (39.3%) receiving onabotA and 27 pts (45.0%) receiving placebo. Treatment-related AEs were reported for both onabotA (arthralgia, n = 1 [1.6%]; burning sensation, n = 1 [1.6%]) and placebo (n = 1 [1.7%] each: arthralgia, arthropathy, hypoaesthesia, joint stiffness, joint warmth, muscular weakness); all were mild. Muscle strength evaluations found no decrease from baseline in any knee or ankle extension/flexion measure in either group at any visit.
Conclusion: This exploratory study found no significant between-group differences in primary or secondary efficacy endpoints; improvement from baseline was observed for both treatment groups. Post-hoc analyses found numerically greater improvement for all efficacy endpoints among the PD-Q nociceptive pain subtype that received onabotA versus placebo, suggesting the PD-Q may be useful in identifying onabotA-responsive pts with knee OA pain. Locally administered onabotA (200 U IA) had an acceptable safety profile and did not decrease muscle strength around the knee. Further evaluation of onabotA efficacy among pts with nociceptive knee OA pain is needed to confirm these post-hoc findings.
Disclosure: Funded by Allergan.



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PHYSIOTHERAPIST-DELIVERED EXERCISE AND PAIN COPING SKILLS TRAINING IS MORE EFFECTIVE THAN EITHER INTERVENTION ALONE IN KNEE OSTEOARTHRITIS

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Purpose: Pain is often the primary symptom of knee osteoarthritis (OA) and results from a complex interaction between structural changes, physical impairments and psychological factors. Much evidence supports the benefits of strengthening exercise in this patient population. There is also limited research supporting psychologist-delivered pain coping skills training (PCST), a form of cognitive behavioural therapy, in knee OA. Though typically provided separately, there are potential symptom-, resource- and personnel-advantages of exercise and PCST being delivered together by a single healthcare professional. Physiotherapists are a logical choice to be trained to deliver a PCST intervention as they already have expertise in administering exercise and are cognisant of the need for a biopsychosocial approach to management. This study aimed to investigate whether an integrated 12-week exercise and PCST treatment program delivered by physiotherapists is more efficacious than either program alone in treating pain and physical function in individuals with knee OA.
Methods: The study utilized a 3-arm randomized controlled trial design with measurements taken by a blinded assessor at baseline, 12, 32 and 52 weeks following randomization. Twelve weeks was the primary time

point. Participants with symptomatic and radiographic knee OA were recruited from Melbourne and Brisbane, Australia and randomized to one of three groups (i) Exercise; (ii) PCST; and (iii) Exercise plus PCST. All groups visited a physiotherapist for ten sessions over 12 weeks. Participants also performed home exercise and/or PCST home practice over the trial duration. Primary outcomes were overall average pain in the past week measured using the Visual Analogue Scale (VAS) and self-reported physical function assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcomes included global rating of change, WOMAC pain, VAS pain on walking, muscle strength, functional performance, physical activity levels, health-related quality-of-life and psychological factors. Statistical analyses were performed on an intention-to-treat basis using all randomized participants.

Results: Two hundred and twenty two participants were randomized and 184 (82%) completed the 12-month trial. Baseline characteristics were similar between the groups. For the primary outcomes all groups showed significantly improved VAS pain and WOMAC physical function following treatment (Fig. 1) with no between-group differences for pain. However, the integrated program resulted in significantly greater improvements in physical function compared to either intervention alone at all time points ($p < 0.02$). Benefits of the integrated program over both programs alone were also seen for VAS walking pain, WOMAC pain, self-efficacy and quality-of-life ($p < 0.05$). The integrated program generally showed greater improvements in psychological parameters compared to exercise alone and greater improvements in functional performance compared to PCST alone.

Conclusions: Results of this novel study provide evidence of the benefits of an integrated exercise and PCST program for physical function, pain and a range of physical and psychological outcomes in the short- and longer-term for people with knee OA. This highlights the potential for a new model of care involving physiotherapists. Advantages of using physiotherapists to deliver PCST may include better integration with exercise, increased availability of PCST treatment to those who may not have access to a psychologist, reduced time and cost for patients, and reduced overall costs to the health care system.

Outcome	Change within groups			Difference in change between groups †		
	Exercise only	PCST only	PCST and Exercise	PCST only vs Exercise only	Integrated vs Exercise only	Integrated vs PCST
VAS overall pain (0-100)						
Week 0-12	27.4 (24.3)*	24.9 (21.5)*	31.4 (17.9)*	-1.9 [-8.9, 5.1]	4.7 [-2.3, 11.8]	6.7 [-0.4, 13.7]
Week 0-32	22.5 (26.7)*	22.8 (24.1)*	30.8 (20.1)*	0.5 [-7.6, 8.6]	8.0 [-0.07, 16.1]†	7.6 [-0.5, 15.7]
Week 0-52	24.3 (27.1)*	23.2 (22.0)*	26.5 (22.4)*	-0.5 [-8.5, 7.5]	2.7 [-5.3, 10.6]	3.1 [-4.7, 11.0]
WOMAC physical function (0-68)						
Week 0-12	15.1 (10.9)*	11.2 (10.3)*	19.9 (9.1)*	-4.1[-7.4, -0.9]***	4.2 [1.0, 7.5]**	8.3 [5.1, 11.6]**
Week 0-32	12.4 (12.6)*	11.1 (12.3)*	18.0 (10.5)*	-1.6 [-5.6, 2.4]	4.7 [0.7, 8.7]†	6.3 [2.3, 10.3]**
Week 0-52	15.9 (12.5)*	12.3 (10.7)*	19.1 (10.1)*	-3.4 [-7.1, 0.33]	2.5 [-1.2, 6.1]	5.8 [2.2, 9.5]**

† Positive difference in change between groups favours the first named group in the pairwise comparison while a negative difference favours the second named group

VAS=Visual Analogue Scale, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

*p≤0.001, **p≤0.01, †p≤0.0

Fig. 1. **Mean (SD) change within groups, and adjusted mean [95% CI] different in the change between groups for primary outcome measures**. The latter were estimated with a mixed effects linear regression model in which physiotherapists were treated as random effects and the baseline scores of the outcome variables were entered as a covariate, together with adjustment for the stratification variable of site.

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SAFETY AND EFFICACY OF MM-II, AN INTRA-ARTICULAR INJECTION OF LIPOSOMES, IN MODERATE KNEE OSTEOARTHRITIS. PROSPECTIVE RANDOMIZED DOUBLE-BLINDED STUDY

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Bio-lubrication is a prerequisite for proper joint mobility and is crucial for prevention of degradative changes of the joint. Phospholipids are components of the synovial fluid and are known to serve as natural lubricants of cartilage surfaces. MM-II is a novel intra-articular bio-lubricant made of liposomes suspended in aqueous solution.

Purpose: To test the safety and effectiveness of intra-articular injection of MM-II in osteoarthritic patients compared with intra-articular hyaluronic acid (HA) up to 3 months of follow-up in a preliminary double-blind, randomized clinical study.

Method: Patients with symptomatic unilateral knee OA meeting ACR criteria, with baseline pain on VAS of more than 40 mm and a stage 2–3 Kellgren Lawrence score on X-ray, were recruited. 40 patients were randomized into two groups of 20, to receive a single intra-articular injection of either MM-II or high molecular weight HA (Durolane®). Effectiveness measures included maximal global pain in the target knee, recorded by a 100 mm VAS; WOMAC subscales; OMERACT OARSI responder criteria; PGA, PASS, PAE questions and consumption of paracetamol/acetaminophen.

Paracetamol/acetaminophen was the only authorized rescue medication. Tolerability was assessed by local manifestation defined by an increase in knee circumference of at least 3 cm in the knee circumference, measured at 2 cm above the upper border of the patella or local pain increase of more than 30 mm on a 100 mm VAS. Adverse events were recorded through 90-days of follow-up.

The study was FIM Exploratory non-powered, with descriptive statistics.

Results: All patients completed the study. In the HA group, the mean patient age was 66.2 years, 9 males and 11females, and the average BMI at baseline was 27.4. In the MM-II group, the mean patient age was 63.0 years, 11 males and 9 females, and the average BMI at baseline was 29.3. The average pain at target knee at baseline was 53.1 mm in the HA group and 55.9 mm in the MM-II group.

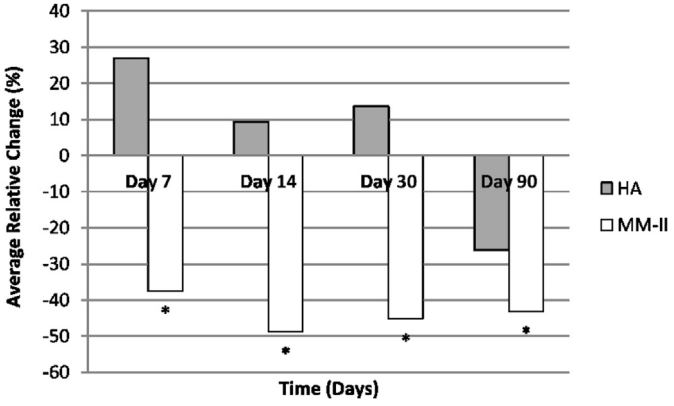
Results relating to WOMAC A pain are summarized in the Fig. 1, and show a faster response with MM-II, with maximal effect observed on day 14, which was maintained over time and was associated with a statistically significant difference from baseline pain from day 7. In the HA group, the onset of pain relief was slower, with an improvement statistically significant change from baseline observed only on day 90.

Daily acetaminophen intake was lower in the MM-II group, with a reduction of more than 50 percent in the number of days and total dose of rescue medication consumption seen following MM-II administration, compared with HA injection.

The percent of responders to treatment according to the OMERAC-OARSI response criteria was 52.6, 66.7, 70 & 60 at the day 7, 14, 30 & 90 respectively compared to 30, 36.8, 25, 45 at the HA group.

Local adverse events (inflammatory flare) were observed in one patient at day 3 in the MM-II group and in 4 patient at day 1, 1 patient at day 3, and 1 patient at day 7 in the HA group.

Patient's Relative Change in WOMAC A in Target Knee over Time



* Statistically significant difference from baseline.

Conclusion: Intra-articular injections of MM-II were found to be safe and effective. The pain-reduction action was more rapid and sustained up to 3 months compared with HA. Larger randomized controlled trials are needed to confirm these encouraging results.